Catalytic Synthesis of Coumarins via Direct Annulations of α,β-Unsaturated Aldehydes and Salicylaldehydes

Ulrike Gross,[a,b] Patrick J. Gross,[a,b] Min Shi,*[b] Stefan Bräse*[a]

[a] Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
E-mail: stefan.braese@kit.edu

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. of China
E-mail: mshi@mail.sioc.ac.cn

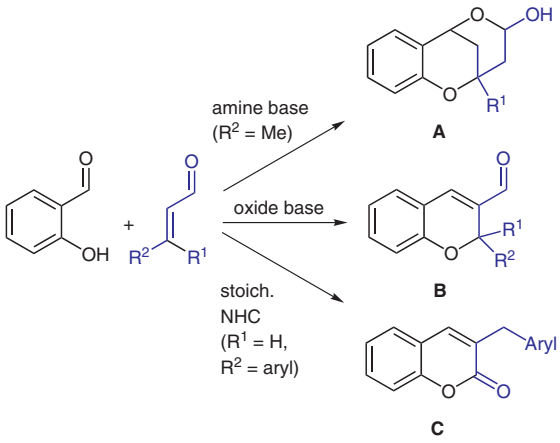
Received 4 December 2010

Abstract: The first organocatalytic approach towards substituted coumarins is reported. Catalytic amounts of in situ generated N-heterocyclic carbenes (NHC) catalyze a one-pot redox esterification of α,β-unsaturated aldehydes with simultaneous aldol condensation.

Key words: domino reactions, heterocycles, umpolung

The application of N-heterocyclic carbenes (NHC) as catalysts and promoters in organic synthesis enables various highly valuable synthetic transformations.[1] Of particular interest is the inversion of classical reactivity (Umpolung),[2] which include benzoin[3] and Stetter reactions.[4] More recent examples are synthesis of γ-butyrolactones,[5] β-lactones[5a] and other esters,[5b] and γ-lactams.[6]

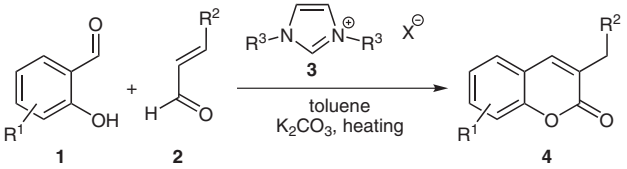
The use of NHC for synthesis of coumarins **C** was described by our group in 2007 (Scheme 1).[7a] It should be noted that depending on the reaction parameters, α,β-unsaturated carbonyl compounds and salicylaldehydes give different reaction products like **A** or **B**.[7b,c]



Scheme 1 Reaction of salicylaldehydes with α,β-unsaturated aldehydes

Earlier we reported the synthesis of benzyl-substituted coumarins **4** (R^2 = Ar) in a one-pot reaction, albeit with stoichiometric amounts of NHC precursors **3** (Scheme 2), large excess of α,β-unsaturated aldehydes **2** and in only moderate yields.[7]

Herein we report our systematic development of an organocatalytic methodology for the synthesis of several coumarins **4** (Scheme 2).



Scheme 2 One-pot synthesis of substituted coumarins **4**[7]

Coumarins are naturally occurring benzopyran derivatives with interesting pharmacological properties.[8] One example is their potential to bind to and activate cannabinoid receptors.[9] Recently, we described the synthesis and biological evaluation of several coumarin derivatives, employing our previously reported NHC-promoted methodology.[10] This way, novel lead structures with high binding activity were identified, showing selectivity towards the cannabinoid receptors CB_1 and CB_2. In a typical procedure salicylaldehyde (**1a**) and 2.5 equivalents of acrolein (**2a**, R^2 = H) were treated with 1.0 equivalent of NHC precursor **3a** [R^3 = Me, X = $(MeO)_2PO_2$] to furnish 26% yield of coumarin **4aa** (R^1, R^2 = H).[7] Similar reaction conditions with cinnamaldehyde (**2b**, R^2 = Ph) furnished only 18% of the product **4ab** (R^1 = H, R^2 = Ph).[7] The use of other α,β-unsaturated aldehydes **2** with R^2 representing an alkyl group had yet been unsuccessful.

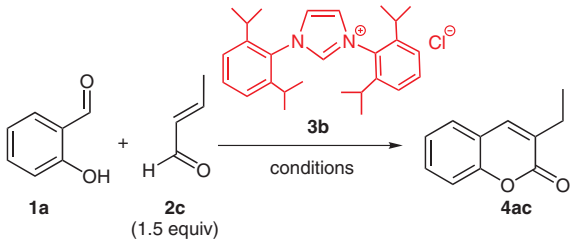
Due to these shortcomings, we decided to further investigate the reaction, to render it more applicable for further synthesis of pharmacological interesting coumarins. Our aim was to lower the loading of NHC precursor **3** to catalytic amounts, to widen the scope of substrates to β-alkyl α,β-unsaturated aldehydes like crotonaldehyde (**2c**, R^2 = Me) and to optimize yields.

We started our screening with salicylaldehyde (**1a**, R^1 = H) and slight excess (1.5 equiv) of crotonaldehyde (**2c**, R^2 = Me) under the previously described conditions (K_2CO_3, toluene, reflux) with different imidazolium and imidazolidinium salts. The best results were obtained with bis(2,6-diisopropylphenyl)imidazolium chloride (**3b**, R^3 = 2,6-diisopropylphenyl, X = Cl), significantly superi-

SYNLETT 2011, No. 5, pp 0635–0638
Advanced online publication: 25.02.2011
DOI: 10.1055/s-0030-1259691; Art ID: G34410ST

or to the previously used 1,3-dimethyl imidazolium species **3a**. These findings are in compliance with results reported for similar reactions: large substituents at the NHC shield reaction intermediates, thus avoiding undesired side reactions.[5] The commercially available, inexpensive imidazolium salt **3b** was used for further optimization. With 1.0 equivalent of **3b**, coumarin **4ac** was obtained in 74% yield (Table 1, entry 1). Lowering the loading of catalyst precursor **3b** diminished the yield to 58% (entry 2). This could be slightly improved by slow addition of crotonaldehyde over six hours (entry 3). Next, different solvents (entries 4 and 5) and bases (entries 6–8) were screened. The application of Cs_2CO_3 proved to be superior to the previously employed K_2CO_3. Further solvent screening, employing Cs_2CO_3 as base, revealed *o*-xylene at 120 °C to be the solvent of choice, furnishing 81% yield (entry 12). Lowering the amount of base to 0.2 equivalents had detrimental effect, diminishing the yield to 56% (entry 13).

Table 1 Optimization of the Catalytic One-Pot Synthesis of Coumarin **4ac**

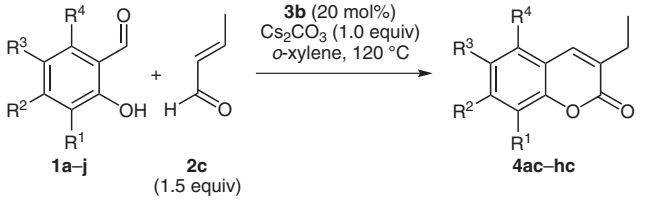


Entry	**3b** (equiv)	Base (equiv)	Solvent	Temp	Yield (%)
1	1.0	K_2CO_3 (1.0)	toluene	reflux	74
2	0.2	K_2CO_3 (1.0)	toluene	reflux	58
3	0.2	K_2CO_3 (1.0)	toluene	reflux	63[a]
4	0.2	K_2CO_3 (1.0)	THF	reflux	67
5	0.2	K_2CO_3 (1.0)	THF–toluene (1:1)	reflux	50
6	0.2	Na_2CO_3 (1.0)	toluene	reflux	65
7	0.2	KO*t*-Bu (1.0)	toluene	reflux	25
8	0.2	Cs_2CO_3 (1.0)	toluene	reflux	68
9	0.2	Cs_2CO_3 (1.0)	THF	reflux	29
10	0.2	Cs_2CO_3 (1.0)	THF–toluene (1:1)	reflux	57
11	0.2	Cs_2CO_3 (1.0)	benzene	reflux	34
12	0.2	Cs_2CO_3 (1.0)	*o*-xylene	120 °C	81
13	0.2	Cs_2CO_3 (0.2)	*o*-xylene	120 °C	56

[a] Slow addition of crotonaldehyde over 6 h.

After the optimization of the reaction conditions,[11] we investigated the scope of the reaction, employing substituted salicylaldehydes **1a–j** (Table 2). Methoxy groups on the salicylaldehyde core are tolerated, although their position had some influence on the yield (entries 2 and 3). Bromine and iodine substituents could be introduced in good yields (entries 4–6), enabling further elaboration of the coumarins, for example, by cross-coupling, which is important for further pharmacological evaluation. Naphthyl derivative **4gc** and biphenyl derivative **4hc** were formed only in moderate yields (entries 7 and 8). In case of **4hc** this could be explained by steric hindrance of the phenol group due to the adjacent phenyl substituent. Using 4-diethylaminosalicylaldehyde **1c**, only starting material was recovered (entry 9). The electron-deficient 5-nitrosalicylaldehyde **1j** led to decomposition (entry 10). This is either due to the decreased nucleophilicity of the intermediate phenolate or due to a higher reactivity of the aldehyde function towards side reactions.

Table 2 Reaction of Different Substituted Salicylaldehydes **1a–j** with Crotonaldehyde **2c**

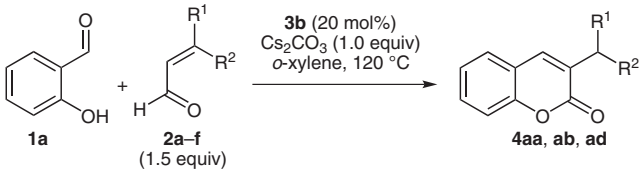


Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	H	H	H	**4ac**	81
2	OMe	H	H	H	**4bc**	74
3	H	H	H	OMe	**4cc**	37
4	OMe	H	Br	H	**4dc**	42
5	H	H	Br	H	**4ec**	79
6	H	H	I	H	**4fc**	67
7	H	(–HC=CH–)$_2$		H	**4gc**	36
8	Ph	H	H	H	**4hc**	33
9	H	NEt_2	H	H	**4ic**	0
10	H	H	NO_2	H	**4jc**	0

Finally we tested the applicability of the optimized catalytic methodology to different α,β-unsaturated aldehydes (Table 3). With acrolein (**2a**, R^1, R^2 = H) under our optimized reaction conditions, but lower temperature (60 °C, due to the higher volatility of acrolein), only 27% of the coumarin **4aa** were obtained (entry 1).

Using 3.0 equivalents of acrolein, which were added subsequently in three portions over six hours, the yield could be increased to 40% (entry 2). The reaction proceeds also with cinnamaldehydes **2c**,**d**, albeit in only moderate yield (entries 3 and 4). With prenal (**2e**, R^1, R^2 = Me) and citral (**2f**, $R^1 = C_6H_{11}$, R^2 = Me) no conversion was observed (entry 5, 6), indicating that β,β-disubstituted aldehydes are no suitable substrates in this reaction.

Table 3 Reaction of Salicylaldehyde **1a** with Different α,β-Unsaturated Aldehydes **2a–f**



Entry	R^1	R^2	Product	Yield (%)
1	H	H	**4aa**	27[a]
2	H	H	**4aa**	40[b]
3	Ph	H	**4ab**	32
4	2-$MeOC_6H_4$	H	**4ad**	47
5	Me	Me	**4ae**	0
6	C_6H_{11}	Me	**4af**	0

[a] 60 °C.
[b] Addition of acrolein (3.0 equiv) over 6 h, 60 °C.

The proposed catalytic cycle for the coumarin formation is outlined in Scheme 3. Deprotonation of imidazolium ion **3b** generates the catalytically active NHC species **7** [R = 2,6-diisopropylphenyl (IPr)], which then adds to crotonaldehyde (**2c**). Tautomerization of the generated zwitterion **5** gives rise to an intermediate, which can be drawn as dienamine **6a** or as its mesomeric homoenolate **6b**. Tautomerization forms the enol **8**, which subsequently undergoes a 1,2-addition to salicylaldehyde (**1a**). The addition product **9** represents an activated carbonyl group, which is prone to intramolecular lactonization. In this step, the catalytically active NHC **7** is regenerated. Cyclization of the alkoxy group of **9** onto the activated carbonyl group would lead to a β-lactone, as observed by Glorius et al. for related structures.[5] In our case, another reaction pathway is possible due to the presence of the phenol group in the substrate: tautomerization of **9** to a phenolate enables lactonization to the δ-lactone **10**. We observed only the formation of the latter, the six-membered-ring lactone and were not able to isolate any β-lactone. Finally, elimination of water under the basic reaction conditions, furnishes coumarin **4b**.

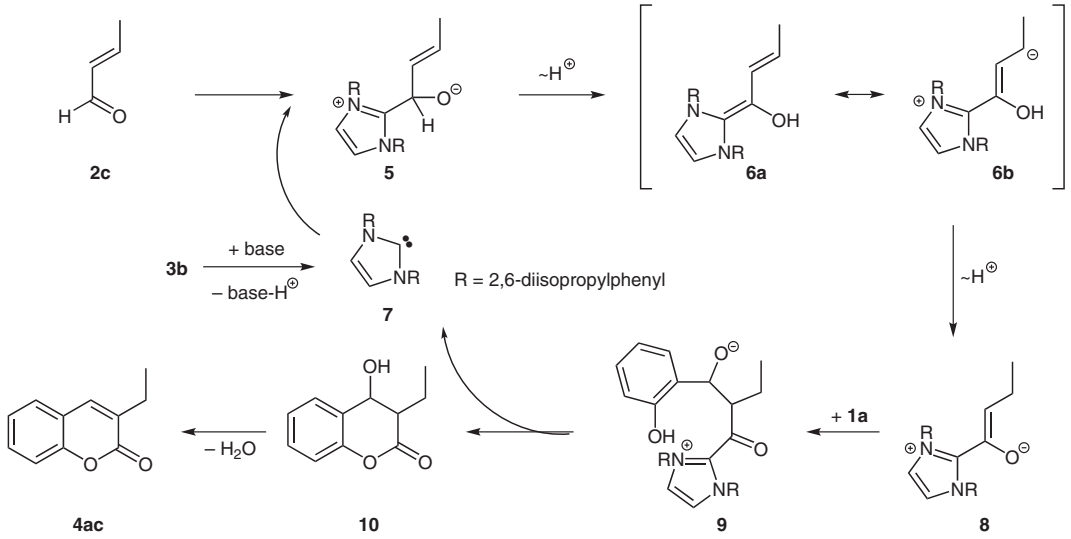
Altogether, the reaction represents a redox esterification of α,β-unsaturated aldehydes with simultaneous aldol condensation. The bond-formation steps are quite unique for NHC-catalyzed reactions, which usually proceed via an a^1-d^1 or a^3-d^3 Umpolung.

In summary, we have developed an organocatalytic methodology for the synthesis of several coumarins. Employing 20 mol% of an inexpensive NHC precursor, the reaction of crotonaldehyde, cinnamaldehydes and acrolein with differently substituted salicylaldehydes proceed in moderate to good yields. This methodology thus allows the readily construction of a variety of coumarins, a family of high interest for pharmacological studies.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. It contains all experimental procedures, including those for the preparation of starting materials, characterization of all compounds and ^1H NMR and ^{13}C NMR spectra.

Acknowledgment

This work was supported by fellowships to U. Gross and P. Gross from the Karlsruhe House of Young Scientists (KHYS) and the DFG [Sino-German program GZ 417(362/1)].



Scheme 3 Proposed catalytic cycle for the reaction of α,β-unsaturated aldehydes with salicylaldehydes to coumarins

References and Notes

(1) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Díez-Gonzáles, S.; Nolan, S. P.; Marion, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (d) Purohit, V. C.; Matla, A. S.; Romo, D. *Heterocycles* **2008**, *76*, 949. (e) Droege, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940. (f) De Sarkar, S.; Studer, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9266. (g) Thai, K.; Wang, L.; Dudding, T.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2010**, *12*, 5708. (h) Du, G.-F.; He, L.; Gu, C.-Z.; Dai, B. *Synlett* **2010**, 2513. (i) Nair, V.; Vellalath, S.; Babu, B. P.; Varghese, V.; Paul, R. R.; Suresh, E. *Org. Biomol. Chem.* **2010**, *8*, 4861. (j) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Jørgensen, K. A. *Org. Lett.* **2010**, *12*, 5052.

(2) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239; Angew. Chem. 1979, 91, 259.

(3) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

(4) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639; *Angew. Chem.* **1976**, *88*, 695.

(5) (a) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418. (b) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (c) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (d) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (e) Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205.

(6) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131.

(7) (a) Toräng, J.; Vanderheiden, S.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 943. (b) Lesch, B.; Toräng, J.; Vanderheiden, S.; Bräse, S. *Adv. Synth. Catal.* **2005**, *347*, 555. (c) Volz, N.; Bröhmer, M. C.; Bräse, S. *Synlett* **2009**, 550. (d) Bröhmer, M. C.; Volz, N.; Bräse, S. *Synlett* **2009**, 1383. (e) For an account, see: Volz, N.; Bröhmer, M. C.; Toräng, J.; Nieger, M.; Bräse, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2009**, *48*, 1699.

(8) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887.

(9) Khanolkar, A. D.; Lu, D.; Ibrahim, M.; Duclos, R. I.; Thakur, G. A.; Malan, T. P.; Porreca, F.; Veerappan, V.; Tian, X.; George, C.; Parrish, D. A.; Papahatjis, D. P.; Makriyannis, J. A. *J. Med. Chem.* **2007**, *50*, 6493.

(10) Behrenswerth, A.; Volz, N.; Toräng, J.; Hinz, S.; Bräse, S.; Müller, C. E. *Bioorg. Med. Chem.* **2009**, *17*, 2842.

(11) **Typical Procedure**
To a round-bottom flask with reflux condenser under argon atmosphere were added salicylaldehyde (20 μL, 23 mg, 0.19 mmol), crotonaldehyde (23 μL, 19 mg, 0.28 mmol, 1.5 equiv), 1,3-diisopropyl-imidazolium chloride (7.0 mg, 37 μmol, 20 mol%), Cs_2CO_3 (60 mg, 0.19 mmol, 1.0 equiv) and *o*-xylene (1.0 mL). The reaction mixture was heated to 120 °C for 12 h. Then H_2O (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 ml), dried over $MgSO_4$, and evaporated under reduced pressure. Purification by chromatography on silica gel, eluting with PE–EtOAc (20:1), yielded the desired product **4ac** (26 mg, 81%) as a pale yellow solid.